analgesia in a mammal upon inhalation comprising:

(a) contacting said substance with COS cells, wherein said COS cells are transfected with a nucleotide vector comprising a nucleic acid molecule encoding ~~an amino acid sequence that is at least 95% identical to~~ (SEQ ID NO:2), wherein said COS cells transiently express said amino acid sequence on a surface of said COS cells, and wherein said amino acid sequence exhibits outward-going potassium rectification; and

(b) determining the potassium transport activity of said amino acid sequence wherein an activation of potassium transport is indicative of said substance having said anesthetic properties.

20. (Twice Amended) A method for identifying substances having anesthetic properties, wherein said substances produce a reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising:

(a) contacting said substance with COS cells, wherein said COS cells are transfected with a nucleotide vector comprising a nucleic acid molecule encoding ~~an amino acid sequence that is at least 95% identical to~~ (SEQ ID NO:4), wherein said COS cells transiently express said amino acid sequence on a surface of said COS cells, and wherein said amino acid sequence exhibits outward-going potassium rectification; and

(b) determining the potassium transport activity of said amino acid sequence wherein an activation of potassium transport is indicative of said substance having said anesthetic properties.

23. (Twice Amended) A method for identifying substances having anesthetic properties, wherein said substances produce a reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising:

(a) contacting said substance with transfected cells, wherein said transfected cells are transfected with a nucleotide vector comprising a nucleic acid molecule encoding ~~an amino~~

~~acid sequence that is at least 95% identical to~~ (SEQ ID NO:5), wherein said transfected cells transiently express said amino acid sequence on a surface of said transfected cells, and wherein said amino acid sequence exhibits outward-going potassium rectification; and

(b) determining the potassium transport activity of said amino acid sequence wherein an activation of potassium transport is indicative of said substance having said anesthetic properties.

REMARKS

We note with appreciation the Examiner's withdrawal of the rejection of Claim 25 under 35 U.S.C. §112, second paragraph. We further note with appreciation the Examiner's withdrawal of the rejection of Claims 14-16, 18, 22, and 25 under 35 U.S.C. §112, first paragraph, and the objection of Claims 19, 20 and 23 under 37 CFR 1.75(C).

Claims 13, 19, 20 and 23, remain rejected under 35 U.S.C. §112, first paragraph. Applicant has amended Claims 13, 19, 20, and 23 to remove proteins having 95% sequence identity with the primary structure of TREK or TASK. Those claims now specify TREK-1 or TASK. Withdrawal of the remaining rejection based on 35 U.S.C. §112, first paragraph is respectfully requested.

Turning now to the merits, Applicants respectfully submit that solicited Claims13-16, 18, 20, 22 and 25 are clearly patentable over Franks and Lieb (Nature, 1994, Vol. 367, pg. 607-614) in view of Fink et al. (EMBO, 1996, Vol. 15, pg. 6854-6862) and/or Duprat et al. (EMBO, 1997, Vol. 16 pg. 5654-5471). Applicants respectfully submit that there is no motivation to combine the teaching of the Franks and Lieb article with either Fink et al. or Duprat et al.

It must be kept in mind under the appropriate test of obviousness under 35 U.S.C. §103 that:

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed.Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id. In re Vaeck* 20 U.S.P.Q. 2d 1438, 1442 (Fed. Cir. 1991).

With this background in mind, the Applicants note with appreciation the Examiner's helpful and detailed statements that "the potassium channel disclosed by Fink et al. *appears* to be the same as the Ik(an) channel of sensitive molluscan neurons." While TREK and TASK may appear to share *some* similar biophysical properties with the Ik(an) channel, a close inspection of Fink et al. by one

skilled in the art reveals that there are still a number of important differences which eliminate any reasonable expectation of success that one of ordinary skill in the art might have.

The Examiner has helpfully pointed to Burgess et al., *Journal of Cell Biology*, 1990, Vol. 111, pg. 2129-2138 and Lazr et al., *Molecular and Cell Biology*, 1988, Vol. 8 pg. 1247-1252, which demonstrates the unpredictable nature of altering amino acid sequences with regard to protein function in the context of 35 U.S.C. §112. Those publications suggest that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein. They also apply with equal force in the context of 35 U.S.C. §103. The amino acid sequence which affects the Ik(an) channel is different from the amino acid sequence which comprises the TREK-1 and TASK proteins, respectively. Based on Burgess et al. and Lazr et al., one skilled in the art would glean that Ik(an) functions differently compared to TREK-1 and TASK, despite appearing to share some similar features. Sharing some features in common does not equate to having the same functionality as demonstrated above.

In that regard, the anesthetic-sensitive K+ channel described by Franks and Lieb (IKAn) is clearly different from TREK-1:

1) TREK-1 displays a kinetic of activation (Maingret et al., 2002. Biochem. Biophys. Res. Commun. 292, 339 -346, Fig. 1) while the Lymnea channel shows no measurable delay in activation (Franks and Lieb, 1988, Nature 333, page 663, lines 1 - 4_;

2) TREK-1 is inhibited in low sodium condition (Fink et al., 1996 EMBO J) while the Lymnea channel is recorded when all the sodium is substituted with TRIS or TEA (Franks and Lieb, 1988, Nature 333, page 662, second column, lines 25 - 26);

3) TREK-1 is opened by arachidonic acid but inhibited by serotonin activation via the cAMP pathway (Patel et al., 1998, EMBO J. 17, 4283 - 4290) while the Lymnea anesthetic-sensitive channel is insensitive to arachidonic acid, serotonin and cAMP injection (Franks and Lieb,

1988, Nature 333, page 664, first paragraph).

Considering these important functional differences, one of ordinary skill in the art would not conclude that TREK-1 and the Lymnea anesthetic-sensitive K+ channel are one and the same. Therefore, we respectfully submit that there is no motivation to combine the teaching of Fink et al. with Franks and Lieb.

TASK-1 is insensitive to chloroform and inhibited by ether (Patel et al., 1999, Nature Neuroscience, 2, 422 - 426, Fig. 2 - 3) while the Lymnea anesthetic-sensitive K+ channel is opened by these inhalational anesthetics (see Franks and Lieb, 1988, Nature 333, page 662, second column, second paragraph). TASK-1 and the endogenous anesthetic-sensitive K+ channel in Lymnea are, thus, different.

As opposed to Franks and Lieb, neither Fink or Duprat et al. suggest that TASK or TREK inactivate with time or respond stereoselectively to the optical isomers of isofluorane. Furthermore, while the Examiner correctly points out that TREK-1 and Ik(an) are "outward rectifying potassium channels", a closer inspection of TREK-1 reveals that it is an "unconventional outward rectifier"(Fink et al., pg. 6859, Column 2 lines 10-35, and pg. 6860 Column 1 lines 1-11). Fink et al. points out that " the molecular mechanisms of the outward rectification for TREK-1 and for 'classical' outward rectifier voltage gated channels [including Ik(an)] belonging to the Shaker superfamily (Kv) are clearly different." Specifically, Fink et al. at pg. 6859, Column 2 states:

> The Kv channels have six TMS and one of them, called S4, contains positive charges which are involved in the voltage sensing of these channels (Logothetis et al., 1992,; Bezanilla and Stefani, 1994). They are activated upon depolarization and opened from a fixed threshold potential whose value depends on the properties of their particular voltage sensor (S4). This threshold potential is always positive in relation to the K^+ equilibrium potential (E_K) and, in physiological conditions, Kv channels only pass outward currents. The TREK-1 structure does not present any domain similar to the positively charged S4 TMS which plays a crucial role in Kv channels. On the other hand, the TREK-1 threshold activation potential is not fixed, and closely follows the E_K. In light of these results, TREK-1 can be referred to as an "unconventional" outward rectifier.

If one skilled in the art were to read Duprat et al., they would recognize that TASK, unlike

Ik(an) and TREK, is highly sensitive to external pH (Duprat et al., pg. 5467, Column 2 lines 9-18). The unique biophysical properties of TASK provide for an unexpected property. One skilled in the art would recognize such an important difference to mean that TASK is clearly not the mammalian equivalent of the molluscan Ik(an) channel. Duprat et al. declares, "the biophysical and regulation properties of TASK are unique" (Duprat et al., pg. 5468, Column 2 lines 23-24). Duprat et al. then goes on to explain the "rectification" differences between TREK and TASK:

> TREK-1 expresses an outward rectification which seems to result from a voltage sensitivity intrinsic to the channel protein (Fink et al., 1996b). In the case of TASK, the outward rectification observed at physiological external K^+ concentrations can be approximated to the rectification predicted by the Goldman-Hodgkin-Katz current equation, suggesting that this rectification simply results from the asymmetric concentrations of K^+ on both sides of the membrane. In other words, this would mean that TASK lacks intrinsic voltage sensitivity and behaves like a K^+- selective "hole". This behavior is, to our knowledge, unique among cloned mammalian K^+ channels. (Duprat, p. 5468, Col. 2).

Logically, it follows that if TREK and TASK are functionally different, as is taught in Duprat et al., then TREK-1 or TASK are different from Ik(an).

Also, the work of Duprat et al. does not show that TASK-1 has biophysical properties that resemble the molluscan S channel or the Lymnea An channel (see Claim 9, end of second paragraph). TASK-1 is inhibited by arachidonic acid while the S channel is opened and the Lymnea channel is insensitive (Patel et al., 1998, EMBO J. 17, 4283 - 4290). Therefore, again, there is no motivation to combine the teaching of Franks and Lieb with Duprat et al.

We also invite the Examiner's attention to *Gambro Lundia AB v. Baxter Healthcare Corp.*, 42 U.S.P.Q.2d, 1378 (Fed. Cir. 1997), which held that the record must show a teaching, suggestion or reason to substitute the claimed invention for the referenced prior art. Applicant submits that this record, and the arguments articulated above demonstrate that there was no suggestion, teaching or reason to substitute TREK-1 or TASK for the Ik(an) channel disclosed in Franks and Lieb with the purpose of identifying substances with anesthetic properties. TREK-1 and TASK exhibit unexpected properties as opposed to Ik(an), and those unexpected properties would cause one skilled in the art

to believe that TREK and TASK are not the mammalian equivalent of Ik(an). Franks and Lieb specifically require a mammalian equivalent and, thus, teach away from a substitute which is not the mammalian equivalent of Ik(an). Franks and Lieb teach an Ik(an) channel or its mammalian equivalent, having all the elucidated properties of molluscan Ik(an) will serve as a prime candidate for general anesthesia. TREK-1 and TASK do not share the elucidated properties of Ik(an) and, thus, did not provide the motivation to combine the teachings of Franks and Lieb with either Fink et al. or Duprat et al. Withdrawal of the 35 U.S.C. §103 rejections is respectfully requested.

In light of the foregoing, we respectfully submit that the claims are in proper form for allowance, which early action is hereby requested.

Respectfully submitted,

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